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PTEN as a Novel Diagnostic and Prognostic Biomarker of Head and Neck Squamous Cell Carcinoma

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Abstract: This review article explores phosphatase and tensin homolog (PTEN)'s role in head and neck squamous cell carcinoma (HNSCC) through comprehensive expression and methylation examinations, genetic mutation investigation, and prognostic evaluation. Using the UALCAN informational collection, PTEN expression examination uncovered a critical over-expression in HNSCC cells isolated from normal control samples, proposing its role in HNSCC multiplication. Further, analysis of PTEN expression across various clinical limits has shown critical up-regulation in different cancer development stages, racial groups, gender, and age classes within the context of HNSCC patients, suggesting its major role in cancer duplication. PTEN expression was validated by utilizing the GEPIA2.0 online tool, which showed PTEN expression was particularly significantly expressed in HNSCC cancer improvement when it appeared differently from normal control samples. Accordingly, examining PTEN validation across different phases of cancer advancement showed dysregulation in each of the four phases with the most raised expression in stage I and the least expression in stage IV. Thus, this study investigated the promoter methylation level of PTEN, figuring out a basic relationship between HNSCC samples and normal control samples. Analyzing promoter methylation across various clinical limits uncovered massive variations, with specific methylation patterns seen across malignant growth stages, race groups, gender, and age groups. Overall survival and disease-free survival (OS and DFS) utilizing the KM plotter tool showed a critical relationship between PTEN expression levels in HNSCC patients, showing high PTEN expression exhibited good overall survival when showed up distinctively comparable to low PTEN expression levels. In addition, in disease-free survival (DFS) evaluation HNSCC patients showing low PTEN expression experienced great DFS relative to HNSCC patients with high PTEN expression. Moreover, to validate PTEN expression against survival, the study examined the HNSCC patients into low and high-expression groups of PTEN. In HNSCC, low PTEN expression was connected with great overall survival (OS) when it appeared contrastingly relative to the high PTEN expression. In like manner, the study found that low PTEN expression level was connected with great DFS in HNSCC when it appeared contrastingly related to the high PTEN expression group. Genetic mutation analysis via cBioPortal identifies a minimal proportion of *PTEN* mutations in HNSCC, predominantly in-frame mutation, missense mutation, splice mutation, truncating mutation, and structural variant, indicating their basal significance in PTEN dysregulation within HNSCC. Further investigation of PTEN molecular components and their exchange inside the HNSCC microenvironment might disclose novel roads for designated treatment and accurate medication approaches in battling this harmful disease.

Keywords: Head and neck squamous cell carcinoma; Diagnosis; Treatment; Biomarker

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1. Introduction

Head and neck squamous cell carcinoma (HNSCC) comprises a group of cancers brought about by the squamous epithelium in the oral epithelium, oropharynx, larynx, and hypopharynx [1]. HNSCC is quite possibly the most well-known cancer and the 6th most common in the world [2]. Approximately 750,000 new cases and 360,000 deaths occur annually [3]. HNSCC represents roughly 3% of new malignant growth cases and 3% of deaths around the world [4]. Roughly 30%–40% of HNSCC patients have early-stage disease (stage I/II) at diagnosis and are typically cured by surgery or radiotherapy (RT) alone [5]. The US recorded around 50,000 new HNSCC cases and 10,000 deaths in 2017. Rates are increasing around 1% a year in whites and over two times as high in men as in women. Early diagnosis of the disease is possibly the main factor leading to less widespread and more effective treatment and better patient outcomes [6]. Tumorigenesis is a complex pathological process that includes multiple genetic changes, including over-expression of oncogenes or inactivation of tumor suppressor genes [7]. Notwithstanding surgery, radiation, and chemotherapy, about half of all patients die from the disease. The risk stratification of HNSCCC relies upon the anatomical site, staging and histological attributes of the cancer. Notwithstanding the situation with HPV, numerous molecular and clinical risk factors have been concentrated that limit its clinical significance [8].

Phosphatase and tensin homolog deleted on chromosome ten (*PTEN*) was initially recognized as a tumor suppressor habitually lost from a region of chromosome 10q23 in different human cancers, including those of the brain, breast, and prostate [9,10]. Until now, the enormous malignant growth data set as of now records > 2700 mutations in PTEN from 28 distinct cancer types and the cBioPortal of The Cancer Genome Atlas (TCGA) records 1120 mutations in 27 cancer types [11,12]. PTEN is a double specific protein and lipid phosphatase, and its essential cell substrate is the second messenger phosphatidylinositol (3,4,5)-trisphosphate (PIP3), which it hydrolyzes to phosphatidylinositol (4,5)-bisphosphate (PIP2) [13,14]. Mounting evidence demonstrates that PTEN additionally has significant PIP3-independent functions. In particular, PTEN protein phosphatase activities are critical for PTEN-mediated inhibition of cellular migration [15]. In glioma cells, it has been shown that the protein phosphatase activity of PTEN is required to actuate PTEN phosphorylation and restrain cellular migration [16]. Besides, there is evidence that PTEN phosphatase activity might regulate glioma cell movement by suppressing Src family kinases [17]. PTEN additionally has nuclear capabilities, which are possibly independent of its ability to antagonize PI3K signaling. Different proteins have been displayed to influence PTEN nuclear localization, subsequently affecting PTEN's ability to act in the nucleus and promote genomic stability [18,19]. In addition to protein regulation, different examinations have shown that PTEN is down-regulated by promoter methylation in thyroid, breast, lung, endometrial, ovarian, gastric, and brain cancers [18].

In the ongoing review, the study explores *PTEN* mutations, expression levels, prognostic outcomes on survival and utilitarian perspectives within the context of HNSCC through bioinformatics assessment. Moreover, the study analyzed the association between PTEN expression and promoter methylation levels. To accomplish this, the study utilized different databases, including The Cancer Genome Atlas (TCGA) data set, the UALCAN portal, the Kaplan-Meier tool, the Gene Expression Profiling and Interactive Analysis GEPIA2.0 and cBioPortal. The major point of this study was to evaluate the PTEN expression patterns in HNSCC and figure out its probable significance in malignant growth treatment and prognosis.

2. Materials and methods

2.1. Expression and promoter methylation analysis of PTEN

To analyze the expression of PTEN, the study used UALCAN online database. The UALCAN data set is a comprehensive, user-friendly, and attractive web resource for analyzing cancer genomics data [20]. It permits users to distinguish Biomarkers or act *in silico* validation of expected genes of interest, assess epigenetic

regulation of gene expression by promoter methylation and perform pan-cancer gene expression analysis. In the current review, this data set was utilized for the expression examination of PTEN across various phases of the predefined malignant growth, in which this gene shows significant dysregulation as well as a critical relationship with worse OS. To examine the promotor methylation level of PTEN in HNSCC, the study utilized a UCALAN data set. The study dissected promoter methylation data of PTEN in various clinical boundaries, such as the patient's age, gender, and race.

2.2. Validation analysis of PTEN

GEPIA2.0 is a widely used online tool for predicting expression and analyzing genomic data survival [21]. The GEPIA 2.0 database can be used to obtain the differences between PTEN expression and prognosis (OS and RFS) in HNSCC cancer patients.

2.3. Survival analysis of PTEN

The KM plotter is a well-known web-based survival analysis tool [22]. It permits scientists to evaluate the relationship between gene expression and survival in different malignant growth types, including breast malignant growth, lung cancer, ovarian cancer, and gastric disease. In this review, the KM plotter tool was utilized to analyze the impact of PTEN dysregulation on cancer patients' overall survival (OS).

2.4. Mutational analysis of PTEN

The cBioPortal for cancer genomics is a platform that permits scientists to access and dissect enormous datasets of cancer genomics information [12]. It provides an easy-to-understand point of interaction for investigating cancer mutations, gene expression and other genomic information across various cancer types. The platform intends to overcome any issues between complex genomic information and cancer specialists by intuitively admitting molecular profiles and clinical attributes. This study utilized this data to perform a mutational examination of PTEN across HNSCC cancer.

3. Results

3.1. Expression analysis of PTEN in HNSCC based on sample types

The study utilized the UALCAN database (**Figure 1**) to analyze the PTEN expression in HNSCC and normal control samples. Upon analysis, the study found critical up-regulation of PTEN expression in HNSCC cancer cells compared with normal control samples. This critical over-expression depicted a close association between PTEN expression and the proliferation of HNSCC cancerous cells.

3.2. Expression analysis of PTEN in HNSCC divided based on different clinical boundaries

Thus, the study facilitated an assessment of PTEN in HNSCC samples across different clinical parameters, including individual cancer stages, patient's race, gender and age (**Figure 2**). From the beginning, the study examined PTEN expression across various cancer development stages and noticed a basic over-expression of PTEN in HNSCC across all stages as contrasted with ordinary control samples (**Figure 2A**). Along these lines, the study assessed PTEN expression in HNSCC patients, revealing critical over-expression of PTEN in all three racial groups, such as Caucasian, African-American and Asian, when contrasted with normal control samples (**Figure 2B**). In addition, the study analyzed PTEN expression in HNSCC patients detached in gender, which showed notable up-regulation of PTEN in both male and female patients when separated from normal control samples (**Figure 2C**). Finally, the study researched the connection between PTEN expression and patient age in HNSCC. The investigation displayed over-expression of PTEN across different age packs among HNSCC patients (**Figure 2D**).

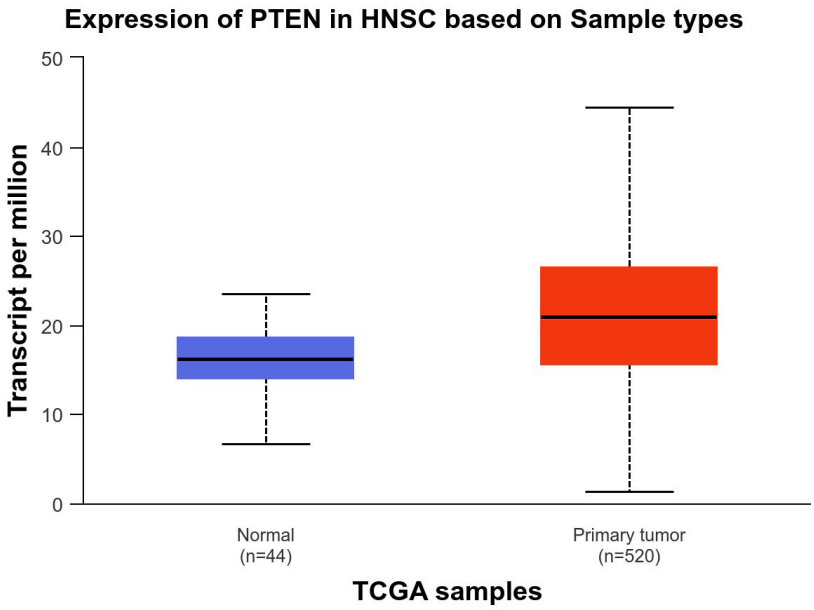

Figure 1. Expression profiling of PTEN in HNSCC and normal tissue samples.

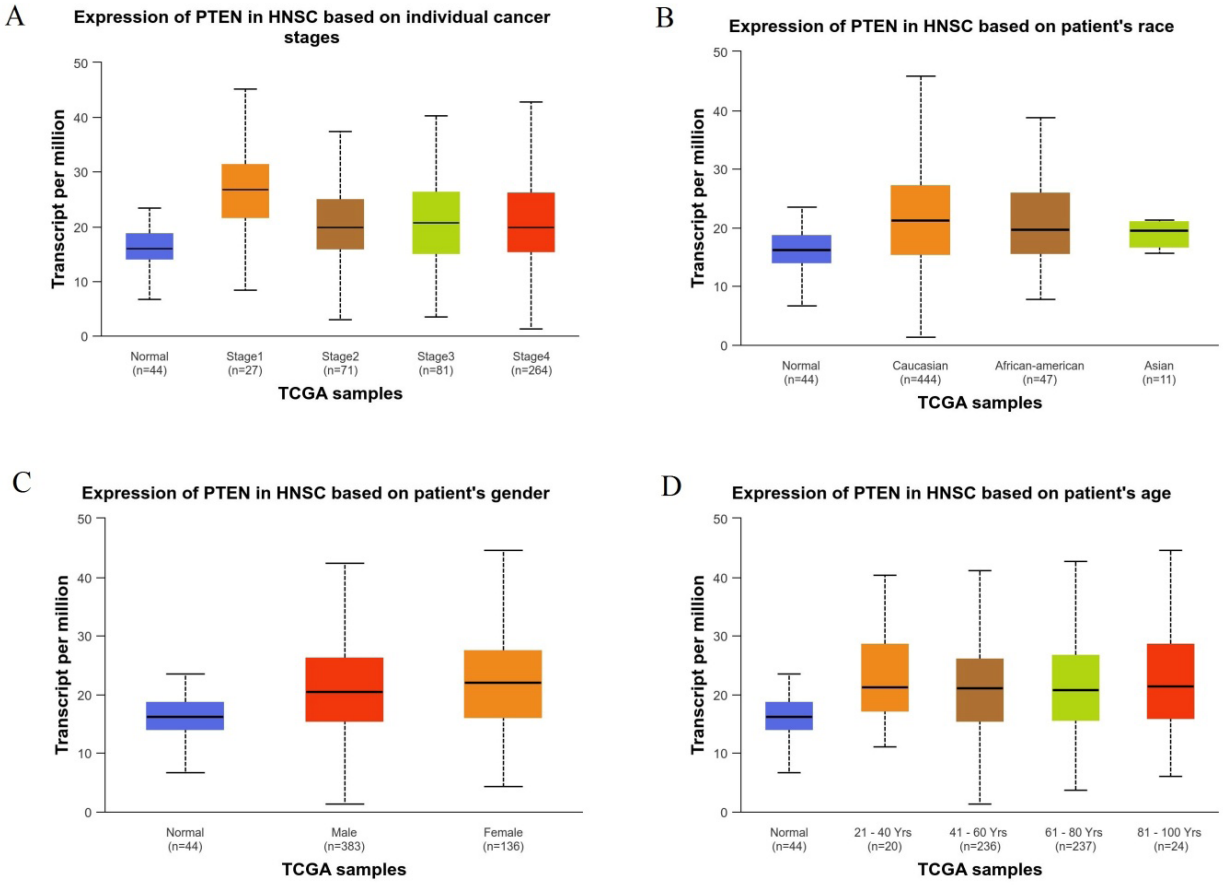

Figure 2. Expression of PTEN across different clinical boundaries.

3.3. Prognostic analysis of PTEN expression in HNSCC

The study used GEPIA2 to examine the PTEN expression between HNSCC cancer when it appeared differently in relation to normal tissues. The result showed that PTEN was especially highly expressed in head and neck squamous cell carcinoma HNSCC compared to normal control samples (**Figure 3A**). In addition, the study segregated the connection between PTEN expression and different cancer stages using the GEPIA2 database. The results showed that PTEN expression was determinedly associated with the phases of patients with HNSCC. In HNSCC, PTEN had the most raised expression in stage I and minimal expression in stage IV (**Figure 3B**).

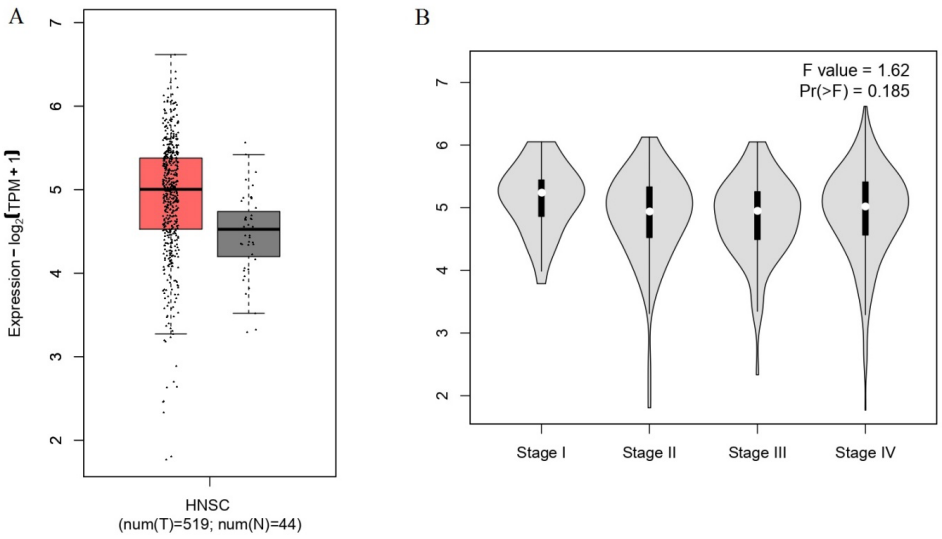

Figure 3. Validation of PTEN expression across different stages of HNSCC.

3.4. Promoter methylation of PTEN in HNSCC and normal control tissues

UALCAN database is utilized to differentiate the promoter methylation of PTEN in HNSCC and normal control samples (**Figure 4**). The study uncovered a significant assortment, expressly hypo-methylation, in the promoter methylation level of PTEN in HNSCC when it appeared differently from normal control samples. This nature proposed potential epigenetic dysregulation of PTEN, featuring its association with HNSCC pathogenesis. Such disclosures add to how the study could unravel the molecular role underlying HNSCC enhancement and idea experiences into the role of PTEN as a potential biomarker or therapeutic agent in HNSCC management.

Figure 4. Promoter methylation pattern of PTEN in HNSCC and normal control samples.

3.5. Promoter methylation of PTEN in HNSCC cancer divided based on different clinical parameters

The study researched different clinical parameters to look at the promoter methylation of PTEN in HNSCC (**Figure 5**). Fundamentally, the study inspected PTEN promoter methylation across various HNSCC cancer stages compared to normal control samples. Critical variations are displayed among stages. In which every one of four phases has shown significant hypo-methylation when contrasted with typical control samples (**Figure 5A**). Subsequently, the study investigated PTEN promoter methylation, considering the race of HNSCC patients. The study found information that hypo-methylation occurred in the PTEN promoter region across every one of the three racial groups, such as Caucasian, African-American and Asian as compared to normal control samples (**Figure 5B**). After this, an assessment of PTEN promoter methylation with females and males showed hypo-methylation (**Figure 5C**). Finally, the study researched PTEN promoter methylation with respect to patient age, uncovering changing methylation levels across various age packs (**Figure 5D**). These comprehensive evaluations highlight the astounding relationship between PTEN promoter methylation and different clinical parameters in HNSCC, investigating understanding the various structures critical in PTEN expression regulation in HNSCC pathogenesis.

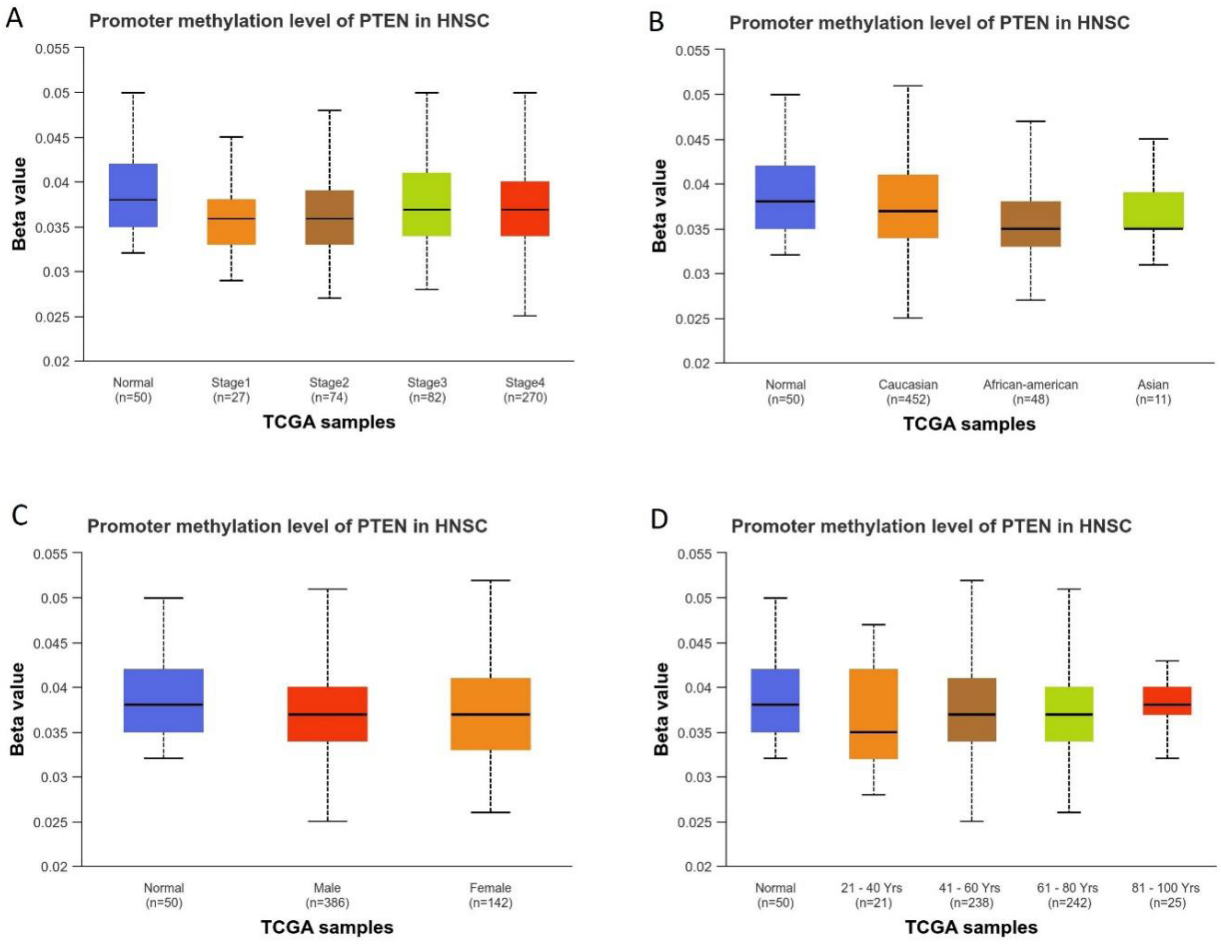

Figure 5. PTEN promoter methylation pattern across different clinical parameters.

3.6. Survival analysis of PTEN

To assess the PTEN gene expression in HNSCC, the study appraised overall survival (OS) and disease-free survival (DFS) using the KM plotter tool. A fundamental affiliation displayed between *PTEN* gene expression and patient survival results in the current review. In particular, HNSCC patients showing high PTEN expression

experienced favorable OS when was shown distinctively with low PTEN expression level (**Figure 6A**). Further, in disease-free survival (DFS) examination, HNSCC patients with low PTEN expression experienced good DFS compared with HNSCC those with high PTEN expression. These findings highlight the vital role of PTEN in influencing the survival results of HNSCC patients, underlying its potential clinical significance as a prognostic marker in HNSCC management.

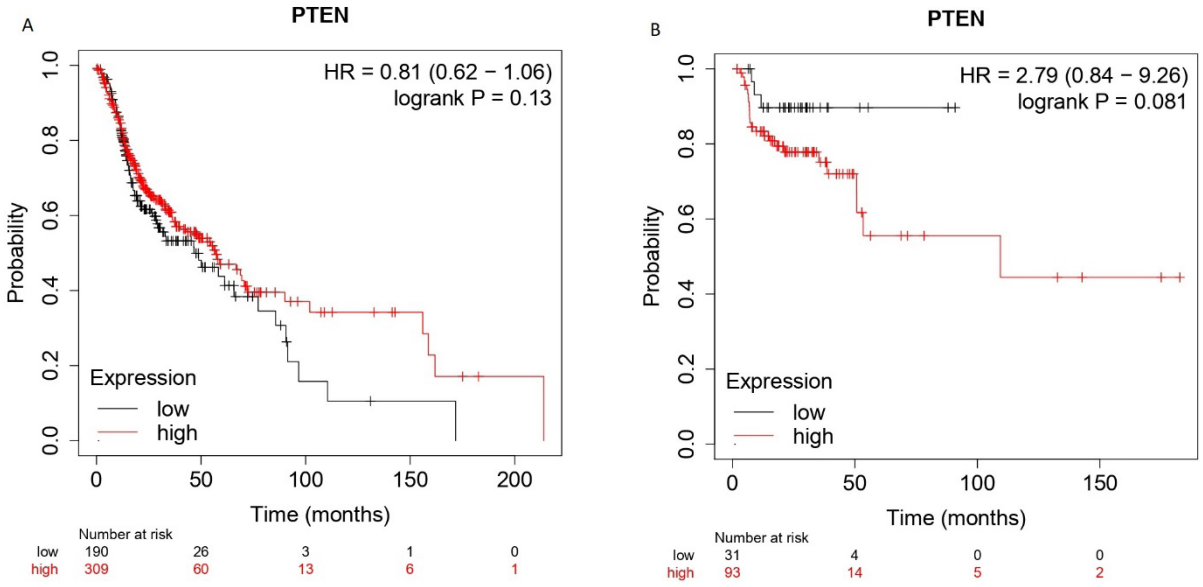

Figure 6. KM survival curve (OS, RFS) of PTEN in HNSCC patients.

3.7. Prognostic analysis of PTEN in HNSCC

The GEPIA2.0 informational index was used to focus on the prognostic worth of PTEN expression in HNSCC disease progression. The study isolated the HNSCC patients into low and high-expression groups of PTEN expression levels. In HNSCC, low PTEN expression was connected with good overall survival (OS) compared to high PTEN expression (**Figure 7A**). Likewise, the study found that a low PTEN expression level was connected with great DFS in HNSCC compared to a high PTEN expression pack (**Figure 7B**).

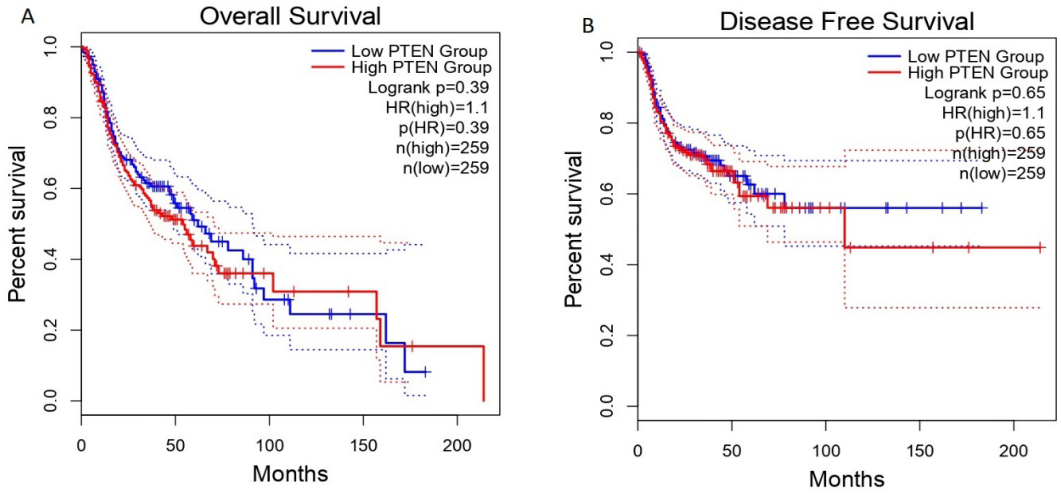

Figure 7. Survival curve (OS, RFS) of PTEN in HNSCC patients.

3.8. Mutational analysis of PTEN

The study further explored the genetic mutations of *PTEN* in HNSCC patients utilizing cBioPortal. The examination uncovered that just 7% of HNSCC samples showed genetic mutations in PTEN. The analyzed genetic mutations in HNSCC included in-frame mutation, missense mutation, splice mutation, truncating mutation and structural variant (**Figure 8**). These discoveries recommend that while genetic mutations in PTEN are generally uncommon in HNSCC, the noticed in-frame mutation, missense mutation, splice mutation, truncating mutation, and structural variant might assume a major part in the dysregulation of PTEN in HNSCC.

Figure 8. Oncoplot of PTEN in HNSCC cancer.

4. Discussion

This review article examined PTEN expression, prognosis, methylation, survival and mutations and drove an assessment in HNSCC using different bioinformatics online devices. In addition, overall survival and DFS were used to validate the differentially expressed significant head and neck squamous cell carcinoma. The outcomes portrayed that PTEN expression fundamentally influences the human body and reason a likely relationship between PTEN expression and HNSCC cancer expansion, proposing PTEN expression as a putative controller in HNSCC pathogenesis.

The incidence of HNSCC is expanding around the world [23]. The 5-year survival rate of patients with HNSCC is less than 50% [24], which is associated with a lack of reliable biomarkers [25]. Recent examinations have laid out a connection between molecular markers, for example, autophagy genes, immune genes, autophagy-related long noncoding RNAs (lncRNAs) and immune-related lncRNAs, and HNSCC prognosis [26,27], which might support in deciding clinical results. As ferroptosis is supposedly involved with both malignant growth progression and cancer suppression, it tends to be a novel therapeutic target for cancers [28]. In that capacity, prognostic ferroptosis-related signature genes have been laid out for different cancers, including hepatocellular carcinoma [29], glioma [30], uveal melanoma [31], and clear cell renal cancer [32]. SLC7A11 is a biomarker and therapeutic target for HPV-positive HNSCC [33]. Moreover, ferroptosis improves the clinical development inhibitory viability of PDT against oral tongue squamous cell carcinoma [34].

PTEN is a very strong and multi-layered cancer suppressor practically associated with a wide range of "hallmarks" of cancer. The principal system by which PTEN activity limits malignant growth development and progression remains its ability to down-modulate signaling through the PI3K pathway, in this manner in a roundabout way repressing AKT downstream targets, like GSK3, FOXO, B cell lymphoma 2 (BCL-2) antagonistic of cell death (BAD), the E3 ubiquitin-protein ligase MDM2 and p27, which control survival, cell multiplication, angiogenesis and cellular metabolism [35]. On the other hand, the mTORC1 arm of the PI3K/AKT/mTOR pathway is likewise actuated in light of the deficiency of PTEN inhibitory activity, bringing about the phosphorylation of p70 ribosomal protein S6 kinase (S6K; otherwise called RPS6K) and restraint of 4E-restricting protein 1 (4EBP1; otherwise called eIF4EBP1) to activate protein translation prompting to the enhanced translation of explicit mRNAs that are critical for cell development and proliferation [36,37]. Recently, 4EBP1 has, without a doubt, emerged as a crucial negative regulator of cell expansion downstream

of mTORC1, and its inactivation may straightforwardly advance the development of inconsistent malignant growths [38,39]. Loss of *PTEN* plays an important role in the development of 30%–60% of melanomas. Evidence has shown that decreased *PTEN* transcript levels were associated with *PTEN* promoter methylation in melanoma [40,41]. Decreased PTEN expression has been shown in pancreatic cancer cell lines, in spite of the fact that deletion or mutations that cause PTEN loss of activity have not been recognized with significant frequency in human pancreatic ductal adenocarcinoma (PDAC) [42]. *PTEN* loss or inactivating mutations are found in a variable proportion (5%–30%) of sporadic colorectal cancers [43–45]. *PTEN* mutations happen at a low frequency in NSCLC and in small cell lung cancer (SCLC), with the notable exemption of squamous cell carcinoma of the lung, in which *PTEN* is mutated in 6–9% of the cases and essentially modified in up to 15% of cases, considering the loss of expression as well [46]. Germline *PTEN* mutation in Cowden syndrome has an inclination to breast malignant growth, where female CS patients have up to 85% LR of developing breast cancer [47–49]. In sporadic breast carcinomas, the frequency of *PTEN* loss is 30%–40% [50].

In the current assessment, the UALCAN database was applied to figure out the expression of PTEN in HNSCC. In the UALCAN assessment, the continuous analysis has shown that up-regulation of PTEN expression was seen in different cancer stages, individual cancer development types, age, gender and racial groups. As to advancement in tumors, the consequence of flow concentrates on portraying that the PTEN expression level was higher in HNSCC tissues than in normal control samples. Besides, in the KM plotter tool, the appraisal uncovered that HNSCC patients showing high PTEN expression experienced good overall survival. HNSCC patients showing low PTEN expression exhibited good DFS compared to low and high PTEN expression. In the examination, it was found that the PTEN expression level in tissue was a poor independent prognostic component. Further evaluations should explore the prognostic worth of PTEN expression in malignant growth development.

5. Conclusion

In conclusion, the analysis indicates that PTEN over-expression in HNSCC is closely associated with poor overall survival, promoter methylation levels, and genetic mutations. Through proper utilization of various public databases, including UALCAN, TCGA, cBioPortal, and KM plotter, the study has thrown light on the diagnostic, prognostic, and potentially therapeutic roles of PTEN in HNSCC. However, further research is required to validate and confirm these findings and explore the underlying mechanisms driving PTEN dysregulation in HNSCC. These findings may ultimately contribute to the development of improved diagnostic tools and therapeutic strategies for HNSCC patients.

Disclosure statement

The authors declare no conflict of interest.

References

[1] Solomon B, Young RJ, Rischin D, 2018, Head and Neck Squamous Cell Carcinoma: Genomics and Emerging Biomarkers for Immunomodulatory Cancer Treatments. Semin Cancer Biol, 52(Pt 2): 228–240.

[2] Vokes EE, Weichselbaum RR, Lippman SM, et al., 1993, Head and Neck Cancer. The New England Journal of Medicine, 328(3): 184–194.

[3] Sung H, Ferlay J, Siegel RL, et al., 2021, Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and

Mortality Worldwide for 36 Cancers in 185 Countries. CA: A Cancer Journal for Clinicians, 71(3): 209–249.

[4] Siegel RL, Miller KD, Jemal A, 2020, Cancer Statistics, 2020. CA: A Cancer Journal for Clinicians, 70(1): 7–30.

[5] Pfister DG, Spencer S, Brizel DM, et al., 2014, Head and Neck Cancers, Version 2. Clinical Practice Guidelines in Oncology. Journal of National Comprehensive Cancer Network, 12(10): 1454–1487.

[6] Chai RC, Lambie D, Verma M, et al., 2015, Current Trends in the Etiology and Diagnosis of HPV-Related Head and Neck Cancers. Cancer Med, 4(4): 596–607.

[7] Vogelstein B, Kinzler KW, 2004, Cancer Genes and the Pathways They Control. Nature Medicine, 10(8): 789–799.

[8] The Cancer Genome Atlas Network, 2015, Comprehensive Genomic Characterization of Head and Neck Squamous Cell Carcinomas. Nature, 517(7536): 576–582.

[9] Li J, Yen C, Liaw D, et al., 1997, PTEN, a Putative Protein Tyrosine Phosphatase Gene Mutated in Human Brain, Breast, and Prostate Cancer. Science, 275(5308): 1943–1947.

[10] Steck PA, Pershouse MA, Jasser SA, et al., 1997, Identification of a Candidate Tumour Suppressor Gene, MMAC1, at Chromosome 10q23.3 That Is Mutated in Multiple Advanced Cancers. Nature Genetics, 15(4): 356–362.

[11] Gao J, Aksoy BA, Dogrusoz U, et al., 2013, Integrative Analysis of Complex Cancer Genomics and Clinical Profiles Using the cBioPortal. Science Signaling, 6(269): 2004088.

[12] Cerami E, Gao J, Dogrusoz U, et al., 2012, The cBio Cancer Genomics Portal: An Open Platform for Exploring Multidimensional Cancer Genomics Data. Cancer Discovery, 2(5): 401–404.

[13] Li DM, Sun H, 1997, TEP1, encoded by a Candidate Tumor Suppressor Locus, is a Novel Protein Tyrosine Phosphatase Regulated by Transforming Growth Factor Beta. Cancer Research, 57(11): 2124–2129.

[14] Stambolic V, Suzuki A, de la Pompa JL, et al., 1998, Negative Regulation of PKB/Akt-Dependent Cell Survival by the Tumor Suppressor PTEN. Cell, 95(1): 29–39.

[15] Leslie NR, Yang X, Downes CP, et al., 2007, PtdIns(3,4,5)P(3)-Dependent and -Independent Roles for PTEN in the Control of Cell Migration. Current Biology, 17(2): 115–125.

[16] Raftopoulou M, Etienne-Manneville S, Self A, et al., 2004, Regulation of Cell Migration by the C2 Domain of the Tumor Suppressor PTEN. Science, 303(5661): 1179–1181.

[17] Dey N, Crosswell HE, De P, Parsons R, Peng Q, Su JD, et al., 2008, The Protein Phosphatase Activity of PTEN Regulates SRC Family Kinases and Controls Glioma Migration. Cancer Res, 68(6): 1862-1871.

[18] Song MS, Salmena L, Pandolfi PP, 2012, The Functions and Regulation of the PTEN Tumour Suppressor. Nature Reviews Molecular Cell Biology, 13(5): 283–296.

[19] Mayo LD, Donner DB, 2002, The PTEN, Mdm2, p53 Tumor Suppressor-Oncoprotein Network. Trends Biochem Science, 27(9): 462–467.

[20] Chandrashekar DS, Bashel B, Balasubramanya SAH, et al., 2017, UALCAN: A Portal for Facilitating Tumor Subgroup Gene Expression and Survival Analyses. Neoplasia, 19(8): 649–658.

[21] Tang Z, Kang B, Li C, et al., 2019, GEPIA2: An Enhanced Web Server for Large-Scale Expression Profiling and Interactive Analysis. Nucleic Acids Research, 47(W1): W556–W560.

[22] Maciejczyk A, Szelachowska J, Czapiga B, et al., 2013, Elevated BUBR1 Expression Is Associated with Poor Survival in Early Breast Cancer Patients: 15-Year Follow-Up Analysis. J Histochem Cytochem, 61(5): 330–339.

[23] Bray F, Ferlay J, Soerjomataram I, et al., 2018, Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: A Cancer Journal for Clinicians, 68(6): 394–424.

[24] Canning M, Guo G, Yu M, et al., 2019, Heterogeneity of the Head and Neck Squamous Cell Carcinoma Immune Landscape and Its Impact on Immunotherapy. Frontier in Cell and Developmental Biology, 2019(7): 52.

[25] Chow LQM, 2020, Head and Neck Cancer. The New England Journal of Medicine, 382(1): 60–72.

[26] Chen Y, Luo TQ, Xu SS, et al., 2021, An Immune-Related Seven-lncRNA Signature for Head and Neck Squamous Cell

Carcinoma. Cancer Medicine, 10(7): 2268–85.

[27] Yang C, Mei H, Peng L, et al., 2020, Prognostic Correlation of an Autophagy-Related Gene Signature in Patients with Head and Neck Squamous Cell Carcinoma. Computational and Mathematical Methods in Medicine, 28:7397132.

[28] Wang Y, Wei Z, Pan K, et al., 2020, The Function and Mechanism of Ferroptosis in Cancer. Apoptosis, 25(11–12): 786–798.

[29] Liang JY, Wang DS, Lin HC, et al., 2020, A Novel Ferroptosis-Related Gene Signature for Overall Survival Prediction in Patients with Hepatocellular Carcinoma. International Journal of Biological Sciences, 16(13): 2430–2441.

[30] Zhuo S, Chen Z, Yang Y, et al., 2020, Clinical and Biological Significances of a Ferroptosis-Related Gene Signature in Glioma. Frontier of Oncology, 10(590861).

[31] Luo H, Ma C, 2021, A Novel Ferroptosis-Associated Gene Signature to Predict Prognosis in Patients with Uveal Melanoma. Diagnostics, 11(2).

[32] Mou Y, Wu J, Zhang Y, et al., 2021, Low Expression of Ferritinophagy-Related NCOA4 Gene in Relation to Unfavorable Outcome and Defective Immune Cells Infiltration in Clear Cell Renal Carcinoma. BMC Cancer, 21(1): 020–07726.

[33] Hémon A, Louandre C, Lailler C, et al., 2020, SLC7A11 as a Biomarker and Therapeutic Target in HPV-Positive Head and Neck Squamous Cell Carcinoma. Biochemical and Biophysical Research Communications, 533(4): 1083–1087.

[34] Zhu T, Shi L, Yu C, et al., 2019, Ferroptosis Promotes Photodynamic Therapy: Supramolecular Photosensitizer-Inducer Nanodrug for Enhanced Cancer Treatment. Theranostics, 9(11): 3293–3307.

[35] Manning BD, Cantley LC, 2007, AKT/PKB Signaling: Navigating Downstream. Cell, 129(7): 1261–1274.

[36] Ciuffreda L, Di Sanza C, Incani UC, et al., 2010, The mTOR Pathway: A New Target in Cancer Therapy. Current Cancer Drug Targets, 10(5): 484–495.

[37] Ma XM, Blenis J, 2009, Molecular Mechanisms of mTOR-Mediated Translational Control. Nature Reviews Molecular Cell Biology, 10(5): 307–318.

[38] Dowling RJ, Topisirovic I, Alain T, et al., 2010, mTORC1-Mediated Cell Proliferation, but Not Cell Growth, Controlled by the 4E-BPs. Science, 328(5982): 1172–1176.

[39] She QB, Halilovic E, Ye Q, et al., 2010, 4E-BP1 is a Key Effector of the Oncogenic Activation of the AKT and ERK Signaling Pathways that Integrates Their Function in Tumors. Cancer Cell, 18(1): 39–51.

[40] Hollander MC, Blumenthal GM, Dennis PA, 2011, PTEN Loss in the Continuum of Common Cancers, Rare Syndromes and Mouse Models. Nature Reviews Cancer, 11(4): 289–301.

[41] Mirmohammadsadegh A, Marini A, Nambiar S, et al., 2006, Epigenetic Silencing of the PTEN Gene in Melanoma. Cancer Research, 66(13): 6546–6552.

[42] Aguirre AJ, Brennan C, Bailey G, et al., 2004, High-Resolution Characterization of the Pancreatic Adenocarcinoma Genome. Proceedings of the National Academy of Sciences of the United States of America, 101(24): 9067–9072.

[43] Zhou XP, Loukola A, Salovaara R, et al., 2002, PTEN Mutational Spectra, Expression Levels, and Subcellular Localization in Microsatellite Stable and Unstable Colorectal Cancers. The American Journal of Pathology, 161(2): 439–447.

[44] Frattini M, Signoroni S, Pilotti S, et al., 2005, Phosphatase Protein Homologue to Tensin Expression and Phosphatidylinositol-3 Phosphate Kinase Mutations in Colorectal Cancer. Cancer Research, 65(23): 11227.

[45] Naguib A, Cooke JC, Happerfield L, et al., 2011, Alterations in PTEN and PIK3CA in Colorectal Cancers in the EPIC Norfolk Study: Associations with Clinicopathological and Dietary Factors. BMC Cancer, 11(123): 1471–2407.

[46] Dearden S, Stevens J, Wu YL, et al., 2013, Mutation Incidence and Coincidence in Non-Small-Cell Lung Cancer: Meta-Analyses by Ethnicity and Histology (mutMap). Annals of Oncology, 24(9): 2371–2376.

[47] Eng C, 2003, PTEN: One Gene, Many Syndromes. Human Mutation, 22(3): 183–198.

[48] Mester JL, Moore RA, Eng C, 2013, PTEN Germline Mutations in Patients Initially Tested for Other Hereditary Cancer Syndromes: Would Use of Risk Assessment Tools Reduce Genetic Testing? Oncologist, 18(10): 1083–1090.

[49] Marsh DJ, Coulon V, Lunetta KL, et al., 1998, Mutation Spectrum and Genotype-Phenotype Analyses in Cowden Disease and Bannayan-Zonana Syndrome, Two Hamartoma Syndromes with Germline PTEN Mutation. Human Molecular Genetics, 7(3): 507–515.

[50] Zhang HY, Liang F, Jia ZL, et al., 2013, PTEN Mutation, Methylation and Expression in Breast Cancer Patients. Oncology Letters, 6(1): 161–168.